

S rial No. 08/484,836
Attorn y Dkt. 76333/108

30 is directed to a method of the instant invention wherein the polynucleotide is stably integrated into the genome in the treated subject. New claim 31 is directed to a method of the instant invention wherein the polynucleotide is not integrated into the genome in the treated subject. A chart displaying the correspondence between the claims of the instant invention and the claims filed in the parent application, U.S. Serial No. 08/136,079, is included as Appendix 2.

DOUBLE PATENTING

The examiner has provisionally rejected claims 1-29 under 35 U.S.C. §101 as claiming the same invention as that of claims 1-5, 7-10 and 13-28 of co-pending application Serial No. 08/136,790. Applicants believe that the examiner intended the indicated Serial No. to be 08/136,079, the parent application to the instant Continuation-In-Part application.

Applicants maintain that the pending claims are not drawn to identical subject matter of the parent application for two reasons. First, the claims allowed in 08/136,079, as set out at Appendix 1, contain amendments that are not present in the instant pending claims. Second, the instant application is directed to methods and pharmaceutical compositions that employ inducible and radioinducible transcriptional regulatory sequences, as well as stable integration of the polynucleotide. The pending claims are not the same invention, therefore, as the claims to issue in the parent application. Applicants request that the double patenting rejection be withdrawn.

ENABLEMENT

The examiner has rejected claims 1-31 under the first paragraph of 35 USC § 112 because he alleges that the specification fails to adequately teach how to make and use the invention (i.e., fails to provide an enabling disclosure). More specifically, the examiner alleges that "[t]he field of the

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invention, *in vivo* gene therapy to confer normal tissue protection from treatment-related toxicities, is an emergent technology that is both unpredictable and not well-established. . . . It would not be possible for one of ordinary skill in the art to use this invention as described in the specification to provide therapeutic levels of radioprotection or chemotherapeutic protection without undue experimentation."

Applicant hereby incorporates by reference, in their entirety, each of the following documents filed in the parent '079 application: (1) the arguments addressing the rejections under 35 U.S.C. §112, first paragraph in each of the September 6, 1995 and April 1, 1996 Responses, reproduced at Appendix 3; (2) the Declaration of Dr. Joel Greenberger submitted on September 6, 1995, reproduced at Appendix 4; and (3) the Declaration of Dr. Michael Lotze submitted on April 1, 1996, reproduced at Appendix 5.

The enablement allegations are unfounded in view of (1) the instant specification's *in vivo* animal models; (2) the data provided in the Declaration of Dr. Greenberger as well as the Declaration by expert, Dr. Michael Lotze, submitted in the parent application '079 and (3) the data provided in a second Declaration of Dr. Greenberger and a second Declaration by expert Dr. Michael Lotze.

Further proof that the method of the claimed invention does provide therapeutic levels of radioprotection or chemotherapeutic protection is present in a declaration of the inventor, Dr. Joel S. Greenberger, filed under 37 C.F.R. § 1.132. Applicant will submit the final executed declaration shortly. This second Greenberger Declaration provides additional *in vivo* data from the inventor's laboratory showing that the delivery of the MnSOD or Copper/Zinc superoxide dismutase (Cu/Zn) transgene into the lung decreases alveolitis/fibrosis. This evidence shows that a third parameter of radiation damage is decreased using the method of the claimed invention. Figure one provides further support that another radioprotective transgene, Cu/Zn, provides therapeutic

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levels of radioprotection within the context of the claimed invention. In addition, the data in Figure one also shows that the delivery of the transgene is achieved using an adenovirus vector.

The results of applicant's experiments presented in Figure 1 demonstrate that the late effects of irradiation damage in the lung, such as alveolitis/fibrosis, are protected in Nude mice given adenovirus containing human MnSOD. The absence of alveolitis and fibrosis after this therapy, along with the biochemical and molecular biologic data presented in the Declaration by Dr. Greenberger, are clearly suggestive of biochemical (TGF- β), molecular biologic (IL-1, TGF- β by RT-PCR) and histological/anatomical evidence of a protective effect of the human MnSOD transgene expression delivered by intratracheal injection 24 hours prior to irradiation of mouse lungs *in vivo*. It is likely that the decreased lung toxicity lead to the encouraging data showing improved survival and an absence of late structural effects of radiation.

Applicant's data would allow one of skill in the art to determine the dose of either adeno-associated virus or other liposome vectors to achieve the level and duration of expression of a transgene needed for *in vivo* gene therapy. Applicant has presented data on adeno-virus and on liposomes injected intratracheally to obtain a therapeutic effect. Figure 1 shows that adenovirus carrying the MnSOD or Cu/ZnSOD genes provide radiation protection against the late lesion of chronic alveolitis. The doses shown would provide guidance to those of skill in the art to compare this dose of adenovirus, with a dose-response curve of AAV or liposome vectors to achieve the same endpoint. The data relating to pathologic lesions in Nude mice at 132 days, for each of the varying doses of AAV or liposome, could be correlated to the dose used for adenovirus to provide the same effect.

Furthermore, those skilled in the art of gene therapy could use applicant's data on polynucleotides encoding Cu/ZnSOD and

MnSOD to assess polynucleotides other than the gamma glutamyl transpeptidase, manganese superoxide dismutase, metallothionein or copper/zinc superoxide dismutase. The data on Cu/ZnSOD or MnSOD could easily be applied to other radiation protection gene products that interact with toxic species, such as catalase, α 1-antitrypsin, bleomycin hydrolase, peroxidases (e.g., glutathione peroxidase) and proteases. Several of these genes have been reviewed in a paper by Tasan, *Proc. Soc'y Exper. Biol. & Med.*, 203: 286 (1993). A variety of radiation protection polynucleotides encoding gene products known to protect against chemically induced DNA damage, including O⁶-Alkylguanine-DNA, Alkyltransferase, could also be applied to this strategy using data initially provided in the instant disclosure using MnSOD as well and the Declaration under Rule 132 using Cu/ZnSOD. The data also could be applied to inserting transgenes for neutralization of cytokines which can cause pulmonary damage. See Rubin et al., *Int. J. Radiat. Oncol. Biol. & Phys.*, 33: 99 (1995). In summary, the techniques and the data shown by applicant with respect to MnSOD and Cu/ZnSOD in the adenovirus model can be extrapolated readily to use of other radiation-protective genes.

The instant specification would be understood by those skilled in the gene therapy art to utilize vehicles other than liposomes and replication-defective adenoviruses. Numerous other vectors have been shown to deliver transgenes to hematopoietic cells, as well as cells of the liver, skin, and other tissues *in vitro*. As a general method of gene transfer, while the efficiency and reproducibility may vary between vectors, success and delivery of a gene by one vector usually translates to delivery of that same gene by another vector, provided the adequate receptors for that new second vector are present on the cell of interest. For example, adenovirus-mediated transfer of genes to deliver cells (Lieber et al., *PNAS* 92: 6210 (1995); Li et al., *J. Cancer Research* 95: 768 (1995)) can be extended to the use of other vectors to deliver these same genes to the liver. Although adenovirus use in the liver has been the most common,

other vectors have been used for liver transfer, including liposomes. Another striking example involves hematopoietic cells. While a dominant form of viral vector used for gene transfer to hematopoietic cells has been the retroviral vector, numerous papers have shown that other vectors can, with varying efficiency, also be effective vectors for transfer of genes to hematopoietic cells including herpes virus and adenovirus. Thus, success with one vector in a particular system showing a biological effect can reliably be extended to allow one of skill in the art to use another viral vector system for expression of the same gene to obtain the same effect. Thus, vehicles other than liposomes and replication-deficient adenovirus, can be used to practice the claimed gene therapy method.

The instant specification provides guidance administering the described vectors to sites other than directly to organs containing tumor in cancer patients. The essence of the instant disclosure is that the delivery of genes to organs containing tumor protects normal tissues in those organs. While the initial invention is designed to provide for a greater therapeutic ratio in cancer patients, the invention has wide applicability to large numbers of patients without cancer. In particular, the same adenovirus-type vectors can be used to express anti-inflammatory protein genes in the lung or even more dramatically, to deliver the cystic fibrosis transmembrane conductance receptor to the nasal epithelium of patients with cystic fibrosis. The same vectors can be used to deliver the $\alpha 1$ anti-trypsin gene into a patient's lungs in those cases where there is a genetic disorder of expression of this gene. The data provided by applicant showing protection in normal tissues as well as a tumor model, is as applicable to cancer patients as it is to non-cancer patients. In both, the target for the expression is the normal tissue.

Individuals having pre-existing immunity to adenoviral protein do not necessarily inhibit an initial administration of adenoviral vector. A variety of adenoviral vectors have been

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designed, and several of these have been used by applicant. Modification of adenoviral vectors to eliminate the E1 and E2A regions from the vector has been employed to create adenovirus variants to decrease immune response to viral protein. Vectors available and used by applicant in some of his initial experiments, have been designed to minimize the immune response. Those of skill in the art, therefore, would not expect patients with pre-existing immunity to adenovirus to exhibit initial rejection and would use adenoviral vectors that minimize the immune response.

The data support a reasonable expectation of success for treating patients other than cancer subjects. Protection of the lung in cancer patients, as demonstrated by applicant, can reasonably be extrapolated to protection of the lung in subjects with no disease, or patients with cystic fibrosis, $\alpha 1$ anti-trypsin deficiency, or in patients with no pre-existing cancer but who are at high risk for cancer such as those patients who are chronic smokers and may exhibit significant dysplastic reactions in the bronchoepithelium. The extension of this information to other disease categories in other organs, or in normal patients in whom protection from irradiation or cytotoxic injury is required, could reasonably be inferred from the success in applicant's model in which animals are protected from irradiation injury. Since the focus of the present claimed invention is to protect normal tissue, such protection of normal tissue could reasonably be expected to occur in non-cancer patients, as well as cancer patients. Since the genes of interest are those which protect against DNA and cellular damage, such protection would reasonably be expected to occur in the normal tissue of both non-cancer patients and cancer patients.

Applicant submits further evidence that one of ordinary skill in this art would accept our *in vivo* animal data as being indicative of *in vivo* human success. Such evidence is in a declaration by a disinterested expert, Dr. Michael Lotze, filed

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under 37 C.F.R. § 1.132, which states that the disclosed animal data is predictive of human clinical applicability. Applicant will submit the final executed declaration shortly. Dr. Michael Lotze is an expert in the field of gene therapy who has over 9 years experience in Human gene therapy; serves on the editorial boards of *Gene Therapy (Nature)*, *Cancer Gene Therapy* and *Cancer Research, Therapy and Control* and *Cytokines and Molecular Therapy* and is the Co-Director of the Biological Therapeutics Program at the University of Pittsburgh Cancer Institute. The enclosed Declaration by the Dr. Lotze asserts that the animal experiments, which are presented in new Declaration of Dr. Joel Greenberger as well as in the Declaration by Dr. Greenberger filed in the parent '079 application attached hereto as Appendix 4, indicate to those of skill in the art that the claimed method is not only capable of eliciting *in vivo* protection in animals, but also in humans.

Each of the Declarations by Dr. Greenberger and Dr. Lotze offers factual evidence in an attempt to explain why one of ordinary skill in the art would have understood the specification to describe the claimed method and pharmaceutical compositions. The declarations provide statements of fact directly addressing the issue of whether the specification provides an adequate written description to enable the subject matter recited in the claims. The examiner is respectfully requested to consider these declarations that relate to both the enablement and written restriction requirements. *In re Alton*, 76 F.3d 1168, 1174, (Fed. Cir. 1996). The examiner employs a 1995 "NIH Report and Recommendations" to show the unpredictability in the gene therapy art. Applicant's above-discussed evidence rebuts the Examiner's allegations regarding the unpredictability of the art.

In his Declaration of April 1, 1996, Dr. Lotze asserted that applicant's data provides a reasonable expectation of success for therapeutic protection using other protective genes which are capable of neutralizing or eliminating toxic species.

Examples of other protective genes that are known to neutralize or eliminate toxic species, include the following: Copper/Zinc superoxide dismutase, catalase, α 1-antitrypsin, bleomycin hydrolase, peroxidases (e.g., glutathione peroxidase) and proteases.

INDEFINITENESS

Claims 1-31 are rejected under the second paragraph of 35 USC §112 because the examiner believes claim 1 is indefinite regarding the term "a subject." Stedman's Medical Dictionary defines the term subject to mean "an organism which is the object of medical or surgical treatment, experimentation, or dissection," a copy of which is attached as Appendix 7. This reference provides evidence of how those of skill in the art interpret the term subject. In the context of the instant specification, the term subject refers to mammals treated with the gene therapy of the claimed invention. Upon review of the proffered Dictionary definition, applicant respectfully requests that the rejection under 35 U.S.C. §112 be withdrawn.

OBVIOUSNESS

Claims 1-4, 9-12, 14-15 and 18-31 are rejected under 35 USC §103. It seems that the examiner has found claims 5-8, 13, 16 and 17 to be novel and non-obvious in view of the prior art. However, the examiner's rejections are inconsistent because all of the pharmaceutical composition claims 28-31 have been rejected as being obvious.

There are four separate obviousness rejections:

(1) Claims 1, 4 and 20-27 are rejected under 35 USC §103 as being unpatentable over Sorrentino et al. in view of Mulligan; (2) Claims 1-4, 9-12, 14, 18, 20-26 and 28-31 are rejected under 35 USC §103 as being unpatentable over Petkau in view of Alton et al., Jaffe et al. and Wu et al.;

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(3) Claims 1, 4, 9-12, 15, 19-26 and 28-31 are rejected under 35 USC §103 as being unpatentable over Lohrer et al. and Matsubara et al. in view of Mulligan as applied above and

(4) Claims 1-3, 9-11, and 28-31 are rejected under 35 USC §103 as being unpatentable over Hockenberry et al. in view of Mulligan. Applicant hereby incorporates by reference, in their entirety, the arguments in their September 6, 1995 and April 1, 1996 responses filed in the parent '079 application that address the rejections under 35 U.S.C. §103, which are reproduced at Appendix 6.

The claimed invention is not directed to one or more new elements, rather, a new method employing a new combination of elements. In fact, the references cited by the Examiner as disclosing particular elements of the invention do not disclose of the elements of the claimed invention. In addition to the elements addressed in applicant's responses to these same obviousness rejections in the parent application, the examiner fails to address the claimed elements of: (1) a polynucleotide under control of a radioinducible transcriptional regulatory sequence in claim 18

The fourth obviousness rejection of claims 1-3, 9-11 and 28-31 over Hockenberry et al. in view of Mulligan is defective because it applies a October 22, 1993 publication (Hockenberry) that is not available as a reference against the October 15, 1993 filing date of the parent application. The unavailable Hockenberry reference does discuss transfection of the MnSOD cDNA but differs from the instant invention in its aim to stably express MnSOD in vitro, rather than *in vivo*. (Hockenberry et al., page 243, right column and page 249 at "Construction of Plasmids").

In summary, each of the four rejections are improper because the examiner has not shown that the prior art as a whole suggests the desirability to selectively combine the references he has chosen. The examiner presents no line of reasoning as to why the artisan reviewing only the collective teachings of the

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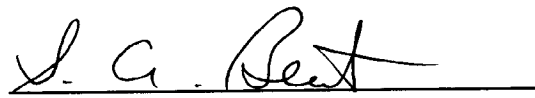
references would have found it obvious to selectively pick and choose various elements from the several references relied on to arrive at the claimed invention. The examiner has done little more than cite references to show that one or more elements or some combinations thereof is known.

Thus, none of the combined references in any of the obviousness rejections address the specific object of the instant invention to provide transient expression of the identified polynucleotides *in vivo*. For these reasons, the claimed invention is not obvious, within the meaning of §103, over the combination of (1) Sorrentino *et al.* in view of Mulligan; (2) Petkau in view of Alton *et al.*, Jaffe *et al.* and Wu *et al.* or (3) Lohrer *et al.* and Matsubara *et al.* in view of Mulligan *et al.*.

In view of the foregoing remarks and the declarations by Dr. Greenberger and Dr. Lotze, it is believed that the application is now in condition for allowance. A speedy and favorable disposition of the application is earnestly solicited.

Respectfully submitted,

9 January 1997
Date


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Appendix 1

Claims Allowed in Parent Application 08/136,079

1. A method for protecting a cancer subject against an agent that elicits production of a toxic species when said subject is exposed to said agent, wherein

- (i) said agent is selected from the group consisting of ionizing radiation, clinical radiation therapy, and a chemotherapeutic drug and,
 - (ii) said toxic species is selected from the group consisting of a free radical, a superoxide anion, and a heavy metal cation,
- said method comprising the step of administering to said subject *in vivo* a pharmaceutical composition comprising
- (A) a polynucleotide that encodes a protein such that, in said subject, said protein is transiently expressed in said subject, wherein said protein (i) interacts with said toxic species to provide a protection therefrom and (ii) is selected from a group consisting of gamma glutamyl transpeptidase, manganese superoxide dismutase, and metallothionein;
 - (B) a pharmaceutically acceptable vehicle for said polynucleotide wherein said vehicle is selected from a liposome and a replication-deficient adenovirus vector; and
 - (C) said administering is directed to the site of the tumor.

2. The method of claim 1, wherein said agent is ionizing radiation.

3. The method of claim 2, wherein said ionizing radiation is clinical radiation therapy.

4. The method of claim 1, wherein said agent is a chemotherapeutic drug.

5. The method of claim 1, wherein said administering is achieved through inhalation.

7. The method of claim 1, wherein said administering is intrarectal.

8. The method of claim 1, wherein said administering is intravesicle.

9. The method of claim 1, wherein said polynucleotide is a cDNA and said vehicle is a liposome.

10. The method of claim 1, wherein said polynucleotide is a cDNA and said vehicle is a replication-deficient adenovirus vector.

13. The method of claim 1, wherein said protein is gamma glutamyl transpeptidase.

14. The method of claim 1, wherein said protein is manganese superoxide dismutase.

15. The method of claim 1, wherein said protein is metallothionein.

16. The method of claim 1, wherein said pharmaceutical composition comprises a mixture of polynucleotides selected from the group consisting of a polynucleotide encoding gamma glutamyl transpeptidase, a polynucleotide encoding manganese superoxide dismutase and a polynucleotide encoding metallothionein.

17. The method of claim 1, wherein said pharmaceutical composition comprises a polynucleotide encoding gamma glutamyl transpeptidase.

18. The method of claim 1, wherein said pharmaceutical composition comprises a polynucleotide encoding manganese superoxide dismutase.

19. The method of claim 1, wherein said pharmaceutical composition comprises a polynucleotide encoding metallothionein.

20. The method of claim 1, wherein said subject is a cancer patient.

21. The method of claim 20, wherein said cancer patient is a lung cancer patient.

22. The method of claim 20, wherein said cancer patient is a prostate cancer patient.

23. The method of claim 20, wherein said cancer patient is a cervical cancer patient.

24. The method of claim 20, wherein said cancer patient is an endometrial cancer patient.

25. The method of claim 20, wherein said cancer patient is an ovarian cancer patient.

26. The method of claim 20, wherein said cancer patient is a bladder cancer patient.

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27. The method of claim 1, wherein said administering is performed prior to said subject's exposure to said agent.

28. A pharmaceutical composition comprising:
(A) a polynucleotide that encodes a protein such that said protein is transiently expressed in a cancer subject exposed to an agent that elicits production of a toxic species selected from the group consisting of a free radical, a superoxide anion, and a heavy metal cation, wherein

(i) said agent is selected from the group consisting of ionizing radiation, clinical radiation therapy, and a chemotherapeutic drug and,

(ii) said protein (a) interacts with said toxic species to provide protection therefrom and (b) is selected from a group consisting of gamma glutamyl transpeptidase, manganese superoxide dismutase, and metallothionein;

and

(B) a pharmaceutically acceptable vehicle for said polynucleotide wherein said vehicle is selected from a liposome and a replication-deficient adenovirus vector.

Claims 6, 11, 12, 29 and 30 were deleted.

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Appendix 2

Claim Correspondence
Between U.S. Serial No. 08/136,079 and 08/484,836

08/136,079 Claims

08/484,836 Claims

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16	16
17	[new claim 17 directed to inducible transcriptional regulatory sequences]
18	[new claim 18 directed to radioinducible transcriptional regulatory sequence]
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24	23
25	24
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27	26
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29	28
30	29
	[new claim 30 directed to stable integration]
	[new claim 31]
	[new claim 31]

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I. "Enablement" Rejection Under § 112

The examiner has rejected claims 1-30 under the first paragraph of 35 USC § 112 because, he alleges, the specification fails to adequately teach how to make and use the invention, i.e., fails to provide an enabling disclosure. More specifically, the examiner alleges that the field of the invention, *in vivo* gene therapy, is an emergent technology that

is unpredictable. See the Office Action at page 2, line 15 and page 4, line 21.

The ultimate question is whether the specification contains a sufficiently explicit disclosure to enable one of ordinary skill in the relevant field to practice the claimed invention without the exercise of undue experimentation. The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key work is *undue*, not *experimentation*. The determination of what constitutes undue experimentation in a case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. See *In re Chilowsky*, 108 USPQ at 325 (CCPA 1960); *In re Woody*, 141 USPQ 518, 520 (CCPA 1964) (even if "no one on earth is certain as of the present whether the process claimed will operate in the manner claimed, . . .

absolute certainty is not required by the law. The mere fact that something has not previously been done clearly is not, in itself a sufficient basis for rejecting all applications purporting to disclose how to do it").

In fact, by routine experimentation implementing the teachings of the instant application, such as Examples 5 and 6, the data provided in the enclosed declarations shows that the claimed method and pharmaceutical composition do provide therapeutic levels of radioprotection. The enclosed unsigned draft of a declaration by the inventor, Dr. Joel S. Greenberger, filed under 37 C.F.R. § 1.132, provides *in vivo* data from the inventor's laboratory employing the method and pharmaceutical composition of the claimed invention. Applicant will submit the final executed declaration shortly. The enclosed data shows that the delivery of the MnSOD transgene into the lung objectively decreases two parameters of radiation damage to the lung. Specifically, serum levels of TGF β and pulmonary levels of both TGF β and IL-1 do not increase to the same extent after radiation exposure, as compared to controls that have not received the protective transgene. In addition, mice that have been given full lung irradiation after MnSOD transgene therapy show improved survival.

Applicant also would address the examiner's specific concerns with regard to enablement of the claimed invention. The examiner is concerned that the duration of expression for adenoviral vectors lasts 2-4 weeks. Such a concern is impertinent to each of the instant claims, which are directed to *transient* expression. The specification defines transient expression at page 11, lines 5-10, as being "finite and...not as extensive as expression resulting from the integration of exogenous DNA sequences into chromosomal DNA." The claimed invention only requires levels and duration of expression that can neutralize or eliminate the toxic ionic species. Therefore, the duration only needs to be long enough to endure the duration of the exposure to the toxic ionic species. The examiner's

concerns regarding the duration and level/dosage should be laid to rest when he recognizes that (1) the claimed method is transient and (2) the enclosed dose-response data illustrates decreased radiation damage and increased survival *in vivo*.

The examiner's concern over the transduction of tumor cell fails to focus on the ultimate objective of the claimed invention: to permit higher doses of radiation therapy or chemotherapy yet decrease the damage to surrounding normal tissue. The examiner believes that the instant invention does not address the possibility of transduction of tumor cells. He finds our disclosure regarding the accessibility to normal versus tumor cells, at page 8 of the specification, to be inadequate because he believes that the protection of even some tumor cells would allow reestablishment of the tumor subsequent to treatment.

Applicant traverses this basis for the rejection for two main reasons. First, the examiner seems to believe that the objective of the instant invention is to effect a cure. In fact, the claimed invention does not itself cure; rather, the companion radiotherapy or chemotherapy produces a cure. The claimed invention is designed to increase the therapeutic ratio of the radiation or chemotherapeutic therapy. By employing the claimed invention, higher doses of radiation or chemotherapeutic therapy can be delivered to the tumor because the claimed method of gene therapy permits the delivery of such increased doses.

Second, since the protective effect is transient, any reestablished tumor will be devoid of the protective effects. The attached declaration of Dr. Greenberger discusses data which shows that mice with orthotopic tumors are protected from irradiation damage by the MnSOD transgene delivery.

In the paragraph bridging pages 4 and 5 of the Office Action, the examiner seems to be question both scope and utility, in the context of urging that clinical success in human beings is not "enabled." The examiner's reliance on the 1991 Ledley reference is misplaced, however, because Ledley is not evidence that animal models provide no indication of clinical success for

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gene therapy. The Ledley publication is directed particularly, to retroviral vectors, which are specifically not claimed in the instant application.

There is no basis in fact that would evidence that applicant's *in vivo* animal data does not indicate *in vivo* human success. The enclosed Declaration by the inventor asserts that the animal experiments presented in the Declaration indicate to those of skill in the art that the claimed method is not only capable of eliciting *in vivo* protection in animals, but also in humans.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Dock t No. 76333/101

In re patent application of

Joel S. GREENBERGER

Group Art Unit: 1804

Serial No. 08/136,079

Examiner: M. Newell

Filed: October 15, 1993

For: PROTECTION FROM IONIZING IRRADIATION OR
CHEMOTHERAPEUTIC DRUG DAMAGE BY IN VIVO GENE THERAPY

REQUEST FOR RECONSIDERATION OF AFTER FINAL REJECTION
UNDER 37 C.F.R. § 1.116

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed December 1, 1995,
please consider the following remarks.

I. ENABLEMENT

A. After Final Enablement Rejection Contains Three New Allegations Not Present in First Office Action. Office Action Should Be Made Non-final With Due Consideration Given to the Declaration of Dr. Lotze.

The enablement rejection is a new ground for rejection, as it is based on three allegations not present in the first office action. The first Office Action merely asserted that "in vivo gene therapy to confer normal tissue protection from treatment-related toxicities, is an emergent technology that is both unpredictable and not well-established. . . . It would not be possible for one of ordinary skill in the art to use this invention as described in the specification to provide therapeutic levels of radioprotection or chemotherapeutic protection without undue experimentation." The enablement rejection presented in the pending Office Action contains three new allegations.

First, Examiner Newell claims that the animal data does not provide a reasonable expectation of success in humans. ("[T]he lack of working examples in the specification regarding in vivo transfer of therapeutically significant level of a therapeutic gene in humans or animals, one skilled in the art would not readily accept on its face in vivo transduction of therapeutic genes at clinically significant levels in any animal without undue experimentation and with a reasonable expectation of success. . . . One skilled in the art would not readily accept the disclosed animal data as correlative of results in human clinical applications based on the state of the art in the field.")

Second, the examiner alleges that liposome-mediated gene transfer in mice provides neither a reasonable expectations of success in non-murine subjects nor a reasonable expectation of success with other transient vector systems. ("One skilled in the art would not readily accept on its face that disclosure of liposome-mediated gene transfer of a therapeutic gene in an animal model would be correlative of therapeutic gene transfer in any and all subjects using any and all transient vector systems.")

Third, the examiner asserts that protection from radiation toxicity by gene delivery of manganese superoxide dismutase in mice provides no reasonable expectation of success for (a) delivery to non-murine subjects, (b) protection from other toxicities and (c) gene delivery of other proteins capable of neutralizing or eliminating toxic ionic species, for example, metallothionein and gamma glutamyl transpeptidase. ("In light of the fact that the toxicities of radiotherapy and chemotherapy are mediated by different toxic agents, and the three protective enzymes of the claimed invention [i.e., manganese superoxide dismutase, metallothionein and gamma glutamyl transpeptidase] act by different mechanisms to neutralize chemically distinct toxic

agents, one skilled in the art would not readily accept on its face that protection from the toxicity of one mode of therapy (radiation) by gene delivery of one protective gene (MnSOD) in a mouse model would be correlative of protection from other distinct mode of therapy (such as chemotherapy) by gene delivery of other protective genes, which neutralize different toxic agents than does MnSOD.")

As the new grounds for challenging the enablement of the instant invention were not presented in the previous office action, applicant urges Examiner Stone to remove the finality of the pending office action. In view of this new basis for rejection, applicant requests that the accompanying Declaration by Dr. Lotze be given due consideration.

B. Three New Enablement Allegations are Unfounded in View of (1) Instant Specification's in vivo Animal Models; (2) Data Provided in Declaration of Dr. Greenberger and (3) Declaration by Expert, Dr. Michael Lotze.

The examiner has rejected claims 1-30 under the first paragraph of 35 USC § 112 because he alleges that the specification fails to adequately teach how to make and use the invention (i.e., fails to provide an enabling disclosure). More specifically, the examiner has made the three allegations outlined above.

The method of the claimed invention does provide therapeutic levels of radioprotection or chemotherapeutic protection. In response to the more general enablement rejection that Examiner provided in his First Office Action, applicant not only pointed to Example six of the instant specification, but also submitted a declaration of the inventor, Dr. Joel S. Greenberger, filed under 37 C.F.R. § 1.132 to provide *in vivo* data from the inventor's laboratory showing that the delivery of

the MnSOD transgene into the lung objectively decreases two parameters of radiation damage to the lung.

Although the examiner appears to have read Dr. Greenberger's declaration, disclosing the *in vivo* (murine) data, he has improperly maintained the enablement rejection by choosing to favor gene-therapy assessments from review articles by Ledley (previously cited) and Marshall (newly cited). Neither of these pertains to the instant invention.

1. Marshall is Not Directed to the Claimed Invention

The examiner's has replaced his reliance on a 1991 Ledley reference with reliance on an August 25, 1995, news article in *Science* 269:1050 by Marshall, as evidence that animal models provide no indication of clinical success for gene therapy. This reliance is flawed. The Marshall publication is not directed particularly to transient gene therapy methods, which are specifically claimed in the instant application. Marshall discusses the fact that most gene therapy protocols are aimed to induce specific cells to produce proteins that would make the cells more vulnerable to attack by the immune system or to act synergistically to potentiate traditional chemotherapy. (*Science* at 1052, middle of second whole paragraph) The instant claimed method achieves just the opposite objective, by rendering the targeted cell less susceptible to attack by chemotherapy.

2. Enablement Rejection's Inclusion of Scope and Utility Rejection is Improper Under the Utility Guidelines

The new enablement rejection is inappropriate in view of the formerly submitted declaration of Dr. Greenberger, which attests that Dr. Greenberger's animal data is predictive of success in humans. Also, the examiner seems to be including a

scope and utility rejection within his concerns that clinical success in human beings is not enabled. Hence, it is improper under the Utility Guidelines, which mandate that a factual showing is needed for a utility rejection and must be provided if a rejection based on the first paragraph of §112 is to be imposed on "lack-of-utility" grounds.

3. Expert Declares the Validity of the Animal Model

There is no basis in fact that would indicate that applicant's *in vivo* animal data does not indicate *in vivo* human success. Applicant submits further evidence that one of ordinary skill in this art would accept our *in vivo* animal data as being indicative of *in vivo* human success. Such evidence is in the Declaration of a disinterested expert, Dr. Michael Lotze, filed under 37 C.F.R. § 1.132, which states that the disclosed animal data is predictive of human clinical applicability. Dr. Michael Lotze is an expert in the field of gene therapy who has over 8 years experience in Human gene therapy; serves on the editorial boards of *Gene Therapy (Nature)*, *Cancer Gene Therapy* and *Cancer Research, Therapy and Control* and *Cytokines and Molecular Therapy* and is the Co-Director of the Biological Therapeutics Program at the University of Pittsburgh Cancer Institute. The enclosed Declaration by the Dr. Lotze asserts that the animal experiments, which were presented in the previous Declaration by Dr. Greenberger, indicate to those of skill in the art that the claimed method is not only capable of eliciting *in vivo* protection in animals, but also in humans.

a) Dr. Greenberger's Animal Models Provide a Reasonable Expectation of Success in Non-Murine Subjects, Including Humans

Dr. Michael Lotze asserts that the liposome-mediated gene transfer in mice provides both a reasonable expectations of success in non-murine subjects as well as a reasonable expectation of success with other transient vector systems. He

readily accepts that the disclosure of liposome-mediated gene transfer of a therapeutic gene in the murine animal model is reasonably predictive of success for therapeutic gene transfer in other animals, including humans. He states, also, that the use of liposome-mediated gene transfer is reasonably predictive of success using other transient vector systems. Dr. Lotze avows that protection from radiation toxicity by gene delivery of manganese superoxide dismutase in mice provides a reasonable expectation of success for delivery to non-murine subjects.

b) Protection from Radiation Toxicity Provides a Reasonable Expectation of Success for Protection from other Toxicities

Further, he declares that protection from radiation toxicity by gene delivery of manganese superoxide dismutase in mice provides a reasonable expectation of success for protection from other toxicities, as in chemotherapy. He bases such a belief on the logic that the toxicities of radiation therapy and chemotherapy both produce radical oxygen species in tissue. Thus, one need only show protection with irradiation to make a reasonable extension of this data logical to chemotherapy. The three protective enzymes of the claimed invention, manganese superoxide dismutase, metallothionein and gamma glutamyl transpeptidase, each act by the same mechanism to neutralize chemically distinct toxic agents. Dr. Lotze indicates that he readily believes that protection from the toxicity of one mode of therapy, such as radiation, by gene delivery of one protective gene (MnSOD) in a mouse model would provide a reasonable expectation for protection from another therapies that produce radical oxygen species, such as chemotherapy.

c) Other Neutralizing or Eliminating Proteins

Dr. Lotze asserts that protection from radiation toxicity by gene delivery of manganese superoxide dismutase in mice

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provides a reasonable expectation of success for gene delivery of other proteins capable of neutralizing or eliminating such toxic ionic species as metallothionein and gamma glutamyl transpeptidase. He found that Dr. Greenberger's data also provides a reasonable expectation for protection using delivery of other protective genes, such as metallothionein or gamma glutamyl transpeptidase. The general applicability of the approach of delivering genes such as superoxide dismutase can be readily applied to other gene products which are capable of neutralizing or eliminating toxic species.

Applicant urges that one of ordinary skill in this art would accept the *in vivo* animal models of the instant specification and the data provided in Greenberger Declaration as being indicative of *in vivo* human success. Further, one such skilled person in this art, Dr. Michael Lotze, does readily accept the *in vivo* animal models as indicating *in vivo* human success.